I. Proposed Core Hypotheses

Exposure to infectious agents during pregnancy and early childhood is associated with the development of schizophrenia and other serious psychiatric diseases in later life.

The risks associated with exposure to infectious agents are modulated by genes which control the immune response to infection as well as genes which control brain development.

The identification of specific infectious agents and predisposing genetic factors can lead to new methods for the prevention and treatment of serious psychiatric disorders.

II. Workgroups

Primary Working Group: Infection, Immunity and Vaccine Working Group.

Potential Collaborating Working Groups:

Development and Behavior
Gene-Environmental Interaction
Early Origins of Adult Health
Pregnancy and the Infant
Repository

III Contact

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IV Public Health Significance

Schizophrenia is a pervasive neuropsychiatric disease associated with altered cognition and behavior. Schizophrenia and related psychiatric disorders are major causes of morbidity and mortality in adolescents and young adults. Population based studies have indicated that approximately 2,200,000 individuals living in the United States will have a diagnosis of schizophrenia or a related disorder during their lifetime. Most individuals with these diseases have their first symptoms during adolescence or early adulthood; almost all of the cases are defined by age 30. Schizophrenia and related disorders are associated with medical costs of approximately $40,000,000 per year and untold costs in terms of personal hardship and family disruption. Individuals with schizophrenia also suffer from a range of somatic health disorders including diabetes and vascular disorders.

Due to these diseases as well as an increased rate of suicide and accidents, individuals with schizophrenia have a substantially shortened life span, with males living 14.1 fewer years and females living 5.7 fewer years than unaffected individuals.

V Need for Cohort Study

The symptoms of schizophrenia are initially subtle and difficult to detect. A prospective cohort study is thus essential in order to provide for the earliest possible detection of cases. In addition, while the positive and negative symptoms which are the hallmark of schizophrenia are generally not apparent until adolescence of early adulthood, retrospective studies have indicated that many individuals with schizophrenia display abnormalities of behavior or cognition in early life. A prospective cohort study which examines these factors provides the only method likely to identify early features of schizophrenia and related disorders. A prospective cohort study would also be the only practical means to assess the role of infections during infancy and childhood in subsequent brain development and associated alterations in behavior or cognition.

Schizophrenia and related disorders have an expected prevalence of approximately 1%. There would thus be expected to be approximately 1000 cases of these diseases in a cohort of 100,000 live births.

VI Scientific Merit

The etiology of schizophrenia has not been precisely determined. Family studies have indicated a strong genetic propensity towards acquiring schizophrenia. However, twin studies indicate that that there is only a 30-50% concordance between monozygotic twins who share almost all of their genetic background. These and other studies indicate that environmental factors also play an important role in the acquisitions of schizophrenia. Epidemiological studies have identified a number of environmental factors related to susceptibility toward schizophrenia. Most of these factors relate to environmental factors operant during pregnancy of early life. These include infections during pregnancy, infections during the neonatal period, winter/spring birth, urban birth, crowding, immigration, and exposure to animals in early life. Specific infections in pregnancy and early life which have been associated with the development of schizophrenia include rubella virus, poliovirus, influenza virus, and other infectious agents. The potential role of infectious agents is supported by a number of animal models which indicate that

Much of the information related to these factors was derived from prospective cohort studies including the Collaborative Perinatal Project (CPP) performed in 11 sites in the United States between 1958-1964. Our group has performed studies with the CPP cohort. We have identified individuals whose mothers were recruited into this cohort, whose births and who developed schizophrenia or a related disorder in later life. We retrieved the corresponding maternal and cord blood samples from the repository and measured markers of infection and antibodies to defined infectious agents. These were compared to

samples from a matched control group without evidence of psychiatric diseases. We found that mothers of individuals who developed schizophrenia in later life had increased levels of total immunoglobulin G and immunoglobulin M as well as several cytokines, including tumor necrosis factor alpha. We also found that mothers of individuals who developed schizophrenia in later life had increased levels of antibodies to Herpes Simplex Virus type 2. Increased levels of antibodies were not found to other human herpesviruses including Herpes Simplex virus type 1, Cytomegalovirus, Epstein Barr virus or Human Herpes Virus Type 6. We also did not find an increased level of antibodies to other sexually transmitted pathogens such as Human Papilloma Virus or *Chlamydia trachomatis*. These findings indicate that in utero exposure to HSV-2 and other infectious agents may be risk factors for the development of schizophrenia in later life.

Data obtainable from the CPP cohort is limited by the methods which were available when that study was performed. In regards to these studies, the CPP cohort did not include obtaining throat swabs, genital samples, or other samples which might be used to test for the replication of an infectious agent. In addition, cytokine measurements were not performed in amniotic fluid samples nor from blood cells obtained from the mothers. The potential role of cytokines and other chemokines in modulating the effect of infections could thus not be completely delineated. Also, samples were not collected for genetic studies. The cohort thus cannot be used for examine gene-environmental interactions. The CPP cohort could thus not be used to examine the potential role of genetic factors such as HLA and cytokine polymorphisms which are known to modulate the immune response as well as genes which control brain development.

Potential for Innovative Research

The finding of an association between infections and serious psychiatric diseases could lead to follow-up studies in which specific interventions were performed in an attempt to prevent or treat disease-causing infections. These studies might consist of vaccines or antimicrobial therapies directed at Herpesviruses, *Toxoplasma gondii*, and other organisms. Studies would determine whether the prevention or treatment of these infections would result in a decrease in the occurrence of schizophrenia and other serious psychiatric diseases. The ability to prevent these devastating diseases would represent a major breakthrough in the management of these diseases and would result in a striking increase in the health and well-being of Americans of all ages.

Feasibility

The prevalence of schizophrenia and related disorders in an unselected population is approximately 1%. These would thus be approximately 1000 cases of these diseases in a cohort of 100,000 live births. The cases would best be identified by the screening of the cohort using standard interviews such as the Brief Psychiatric Rating Scale (BPRS) and other age-appropriate interview-based instruments at defined periods during childhood, adolescence, and early adulthood. This instrument can be administered by appropriately trained study personnel. Cohort members who have abnormal ratings can be referred to medical resources for follow up testing and appropriate treatment. The burden of this

testing could be minimized by having the instruments administered at times of other study visits. The cost would be approximately $10 per testing. (Assuming 0.5 hour of time at a cost of $20/hour). We would anticipate performing 5 interviews during the course of the study for a total coast of $ 50 per participant. It is of note in terms of costs that these interviews might also be employed for the testing of other hypotheses related to neurodevelopment and the occurrence of psychiatric diseases.

There are no risks associated with the BPRS interviews. The subjects would benefit by the early identification of psychiatric disorders and the institution of therapeutic measures directed at the prevention of progression of their disease. Confidentiality would need to be maintained as appropriate for the diagnosis and treatment of psychiatric disorders.

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